

ing in the blood, we find very few facts on which to base a belief. We find ourselves relying solely on what we think has happened in a few apparently similar human cases that have been treated in what we believe to be the same manner. Each one of these cases has been considered apart from any possible control as to what would have happened if no treatment had been given, and each case represents a condition of which we have only the barest conception even under the best conditions in a well-organized hospital. It is true that if we keep our courage up until a hundred cases more or less have done better or worse under this treatment, and if we have made the most minute observations on this series of cases, we may hope to draw some conclusions by comparing them with a similar number of cases treated in other ways and equally well followed. And even then if we find the treatment justified by the results, how may we hope to know from any exact knowledge of the mechanism of the reaction that takes place, how we should modify the treatment to make it more efficient? The plea then is that in applying an experimental method to human beings we should make haste slowly and be patient enough to learn something of the general principle involved, through animal experimentation, before we start to treat individual cases.

In this particular case the experimenter can say little as to the justification for treating a septicemia with bacterial vaccines. It is not easy to see how we can hope to justify it on the ground of provoking any more general reaction as is the case in localized infections. It may, however, be suggested as Smith has done, that the bringing into play of new and unused areas of reaction such as are employed in subcutaneous inoculations might give a reasonable basis of justification in trying this method of treatment.

I think I have sufficiently indicated to you that Wright's method of developing vaccine therapy seems injudicious, although it must be confessed that his popular method has stirred up a general appreciation of the importance of the principle involved. Let us hope that the discrediting of his more visionary ideas on blood coagulation and the opsonic index will not serve to detract from interest in his main thesis of vaccine therapy. In view of these strictures on Wright's method it may seem inconsistent to suggest a possible further improvement of vaccine therapy in human beings. The suggestion, however, is based on results obtained by the methods that have been evolved in active immunization of animals. It has been found that the highest grade of antibacterial immunity is produced by immunizing animals with living rather than with killed bacteria. It has further been found that the best serum to combat an infection like that produced by the bacillus of dysentery is produced by immunizing horses not only against several strains of dysentery bacilli but against the endotoxins of the bacillus. It would be quite feasible to treat human beings with living instead of dead cultures of bacteria at least in the case of those organisms which do not tend to produce generalized infections. We have instances of such inoculation with living cultures in the original and successful method of preventing cholera inaugurated by

Ferran. The use of endotoxins as well as whole bacteria would present no danger over the present method. It seems then quite probable from animal experiments that a more efficient therapeutic reaction to bacterial infections might be induced in human beings by the use of living instead of dead bacteria and by the use of endotoxins in conjunction with the bacterial bodies.

I have often wondered what the present state of mind of the clinician may be in respect to the accepted status of immunity from disease. Facts have accumulated so rapidly that they can scarcely be set in order by one who devotes his entire attention to the subject. The balance of evidence has swung between the cells and the body fluids, first Mechnikoff with emphasis on Phagocytosis, then Pfeiffer, Bordet and Ehrlich with accentuation of the humoral aspects, and last the newer viewpoint of Wright lying half way between, and, in reality, linking the two schools together. It seems to me that Wright with his opsonic theory, was a better harmonizer than he knew. Those bodies known as opsonins, which he insisted on with pardonable pride as *sui generis*, seem now to differ very little from the known antibodies (sensitizers or amboceptors) which were really anticipated by Metchnikoff under the name of "stimulins." Facts seem to be tending to prove that the apparently dual lysins evidenced principally in the test tube, may in the body exert their action as a single body combining the attributes of amboceptor, sensitizer and opsonin, and affecting the bacterium in such a way as to make it more readily devoured by the phagocytes which under normal conditions retain the digestive ferment (cytase, alexin, or complement) that is liberated into the serum under artificial condition. Phagocytosis, then, would be the ultimate and essential process, its completeness depending on the degree of sensitization or opsonization produced extracellularly by the antibodies which are the specific results of immunization. This simplified scheme is I believe consistent with the trend of investigations in immunity.

It would seem, in review, that I have been able to offer little help, except perhaps in the line of simplification and clarification, towards the experimental basis of vaccine therapy. The fault lies as I have said in that the experimental basis of vaccine therapy has been inadequate for a safe prognosis. There remains, however, I hope, no doubt in your minds as to the eventual soundness of the method. I have simply ventured to plead for more scientific conservatism in learning its mechanism as tending toward a greater usefulness.

#### A CLINICAL VIEW OF VACCINE THERAPY.

By HERBERT C. MOFFITT, M. D., San Francisco.

In yielding hesitatingly to the request of the program committee to present in the few minutes at our disposal, the clinical side of the vaccine question my decision was determined by the fact, apparent from observation of the cases of many different men, that lax methods in the application and overenthusiasm in the use of vaccines would tend

\* Read at the Forty-first Annual Meeting of the State Medical Society, Santa Barbara, April, 1911.

naturally to their discredit. Many points in their clinical application are still undecided but it is possible now to formulate certain general rules in regard to preparation, dosage and time of administration. Since the Harvey Lecture of Sir Almroth Wright in 1907 the literature of the subject in our own country has grown extensively. An excellent series of papers by observers in different clinical fields may be found in the Transactions of the Congress of American Physicians and Surgeons, Vol. VIII, 1910. The résumé of Tileston or the more recent one of Stoner (*American Journal of the Medical Sciences*, February, 1911), may be mentioned. Major F. F. Russell has recently given an excellent address upon "The Control of Typhoid in the Army by Vaccination" (*N. Y. State Journal of Medicine*, December, 1910).

**GENERAL CONSIDERATIONS.** There has been much discussion as to the propriety of using vaccines in profound general infections but the brilliant results occasionally observed clinically have shown that with proper precaution their use should be strongly urged. Various theoretical reasons support the results of clinical observation. Kektoen and Carlson have shown that antibactericidal bodies are elaborated in the tissues and not in the blood. Park would emphasize that bacteria in the blood circulate with their antibodies and this may inhibit further production of antibactericidal substances; this would not hold true in the tissues. Theobald Smith has pointed out the possible local character of immune-body production and has suggested the advisability of introducing vaccines into different tissues. Leary strongly supports the view of "the local character of many immunity responses" and advocates injecting vaccines into the muscles. Following the almost universal rule, I have preferred to inject subcutaneously, a convenient place being about the insertion of the deltoid.

**METHOD OF PREPARATION.** The procedure of Wright is well described in the article of Potter and Avery in *Hare's Modern Treatment*. There is a tendency at present toward sterilization at lower degrees of heat with shorter exposures, or to the use of chemical agents as carbolic acid or galactose in place of heat. "Bacterial proteins as well as others lose their specific character by exposure to high temperatures or by prolonged exposure to low temperatures" (Leary). Heating at 55° or 56°, certainly not over 58° for an hour should be advocated; Leishman is killing his typhoid cultures for preparation of vaccine used in the British Army by exposure to 53° for an hour. Weaver and Tunnicliff have demonstrated experimentally that a streptococcus vaccine, prepared by sterilization in 25% galactose solution produced a certain degree of immunity in rabbits while the vaccine sterilized by heat was inert. Vaccines certainly deteriorate with age and a good working rule is to reject all preparations more than 3 months' old.

**SPECIFICITY.** An autogenous vaccine is one made from the specific organism causing the infection in the individual case. It is always to be preferred to heterologous or "stock" preparations. In staphylococcus infections there is not so much objection to the use of stock vaccines as in the case of organisms

like the colon bacillus, pneumococci or streptococci which are subject to much variation through widely differing strains. Nearly all tuberculins are examples of stock vaccines and our treatment of gonorrheal arthritis must usually be carried out with stock preparations. Gilchrist has shown that the staphylococcus albus vaccine may replace the aureus without loss of efficacy.

**DOSAGE.** The method of standardization introduced by Wright is still employed but it does not pretend to any great degree of accuracy and moderate errors in dosage are therefore unavoidable. The number of bacteria to be injected must depend upon the nature of the infection, the virulence of the infective agent, and the resistance of the individual. In acute general infections with profound toxemia only small amounts must be given and the condition of the patient will alone determine the time and amount of subsequent doses. It must be remembered that the degree of immunity produced may bear no relation to the size of the dose, and that large doses in an exhausted organism theoretically may increase toxemia and hasten a fatal issue. There is an undoubted tendency toward reduction of dosage even in local infections without marked systemic reaction, although, on the whole the dangers of large doses have been painted somewhat too vividly. In a case reported by Leary 10,000,000,000 staphylococci were injected by mistake, collapse followed in a few hours but the patient quickly rallied after stimulation. In another individual the same amount produced no reaction at all. Tileston has drawn up a table of dosage based upon the results of many different workers.

	in local infections		in general infections	
Staphylococcus	100,000,000-1,000,000,000			
Streptococcus	5,000,000-200,000,000		5,000,000-25,000,000	
Pneumococcus	10,000,000-200,000,000		20,000,000-50,000,000	
Gonococcus	5,000,000-500,000,000		5,000,000-100,000,000	
Bacillus coli...	10,000,000-200,000,000		10,000,000-50,000,000	

My own experience has taught me caution in beginning treatment with large doses even in chronic infections. I have seen severe pain in the affected kidney follow an initial dose of 20,000,000 colon bacilli. In an interesting case of chronic typhoid bone lesions, inoculation of 40,000,000 bacilli of an heterologous vaccine gave a severe local reaction followed by fever and pronounced malaise and prostration. On the other hand we occasionally fail to see benefit from small doses and obtain prompt improvement from large ones. Three years ago a man entered my service in St. Luke's Hospital after an illness of two months characterized by irregular fever with chills and sweats. Staphylococcus albus was obtained several times in blood and urine cultures. The disease ran a course of weeks with recurrent paroxysms of chills and sweats, irregular pyemic temperature, crops of purpura and variations in size of a large splenic tumor. Ordinary drugs, enemata of collargolum had no effect. During six weeks treatment with an autogenous vaccine in doses of 50,000,000 to 200,000,000 no definite results were noted but after the amount was raised to 600,000,000 and 1,200,000,000 improvement was rapid and only three injections of the larger amount were required. The man has remained perfectly well ever since.

**FREQUENCY OF ADMINISTRATION.** The opsonic

index as a guide to the size and frequency of dosage has not proved of practical value. It may help to determine the nature of an obscure infection or may guide the choice of vaccine in mixed infections. As a rule in acute infections the interval between inoculations should be short and the dose small. In chronic infections an interval of 4 or 5 days has seemed to me better than one of 7 or 10.

**STAPHYLOCOCCUS INFECTIONS.** There can no longer be any doubt of the efficacy of vaccines in the control of local staphylococcus infections. Reports upon the treatment of furunculosis and carbuncles have been almost uniformly favorable. Here as elsewhere autogenous preparations are best but good results may be obtained with stock vaccines. The average dose is 200 to 300,000,000 to be administered every four or five days. Incision, hyperemia induced by application of the Bier cups, dressings of the solution recommended by Wright, 5% sodium citrate with 4% sodium chloride are helpful accessory measures. Staphylococcus albus vaccines have proved of benefit in the treatment of some forms of acne, in sycosis, weeping eczema and other skin affections. Gilchrist has found that superficial acne yields most readily to albus inoculations but the nodular variety due to infection with bacillus acnes requires treatment with autogenous vaccines in small doses 3 to 5,000,000 gradually increased at intervals of 7 to 10 days. In the treatment of chronic sinuses, chronic otitis media or chronic sinusitis due to staphylococcus infection favorable results have been reported. The case of septicemia due to staphylococcus albus has been noted above and one case of recovery from general infection with the aureus (following cellulitis of the hand) has since been observed. In four cases of malignant endocarditis due to the aureus, treatment was begun late in the disease and had no apparent influence on the course of the infection to its fatal termination. Deaver, DaCosta and Pfeiffer reported four recoveries in five cases of staphylococcemia following pelvic abscess, renal abscess, septic endocarditis, abscess of the scalp, pyonephrosis. In three cases of severe toxemia following suppurative nephritis, phlebitis, appendicular abscess recovery was prompt in two cases. From one to six doses of 100,000,000 were required at intervals of 4 to 6 days.

**STREPTOCOCCUS INFECTIONS.** The variability of streptococcic strains makes treatment with stock vaccines, even though polyvalent, much more unsatisfactory than in staphylococcus disease. The more rapid spread of the infection and the more profound intoxication usually accompanying it, make control even by autogenous vaccines less satisfactory. Infected wounds, abscesses, empyema, puerperal septicemia, malignant endocarditis are the conditions the clinician will most often be called upon to treat. In erysipelas no very striking influence has been exerted by vaccines. I have seen two cases get well in about the usual time under treatment with autogenous preparations. It is a disease notoriously of variable virulence in different years and opinions as to efficacy of a particular method of treatment must be uncertain. Important work is being done in preventive inoculations against scarlet fever but it is

yet too early to say whether the method will prove of sufficient value to warrant general introduction. Smith (*Boston Medical and Surgical Journal*, 1910, CIXII, 242), has recently collected the literature on the subject. Weaver concludes from his work with streptococci killed by galatose that injections early in the course of scarlet fever do not prevent later streptococcal complications; subacute and chronic streptococcal complications of infectious diseases are sometimes favorably influenced; acute processes are as a rule unaffected. I have seen two cases of puerperal septicemia apparently marvelously cured by autogenous vaccines; in one case streptococci being cultivated from the blood. One injection of 50,000,000 was given in one case, three injections of 20, 60 and 100,000,000 were given at intervals of 4 days in the other. Leary (*Boston Medical and Surgical Journal*, 1909, CLXI, 741), reported a series of 47 cases with 4 deaths; Hartwell Streeter and Green (*Surgery, Gynecology and Obstetrics*, 1909, IX, 271), reported 18 cases in all of which recovery took place. The favorable result in puerperal cases is probably due to the fact that the chief infection is local and symptoms are due largely to toxemia. Interesting in this connection is the observation of Libman in the study of general infections arising from the complications of otitis media that bacteria disappear from the blood if the local condition is properly controlled. Less favorable results have been reported in the treatment of general streptococcemia though some apparently hopeless cases have been rescued. Da Costa treated two cases of malignant endocarditis and one case of general infection following cellulitis without effect. Wright in 1907 reported six cases of streptococcus endocarditis with 4 deaths. In the collection of Stoner out of 26 cases of acute ulcerative endocarditis 22 were due to streptococcus infection; of the 26 eleven were cured. Six cases of septic endocarditis and one case of streptococcus pyemia were reported by Gilman Thompson (*American Journal of the Medical Sciences*, CXXXVIII, p. 169). "In several of these cases polyvalent vaccines were employed, but without benefit, before homologous vaccines could be obtained, which latter proved effective." Three cases of malignant endocarditis and one of pyemia were cured. The dosage varied from 50 to 300,000,000 and injections were made sometimes on succeeding days, usually at intervals of 5 or 6 days. The writer has seen 2 cases of malignant endocarditis treated with autogenous vaccines in doses of 50 to 100,000,000 without benefit.

Perhaps in future better results may be obtained in streptococcal infections from vaccines sterilized at lower degrees of heat. Leary advocates short exposures to heat and Weaver employs 25% galactose solutions in sterilization with apparent increase in immunizing power. The dose of streptococcus vaccine varies with the severity of this infection. In general infections begin with 5 to 20,000,000 every 2 or 3 days, in local infections larger doses 20 to 50,000,000 may inaugurate the treatment. Subsequent doses of 100 to 200,000,000 may be given and the interval determined by the results on temperature curve and general symptoms.

**PNEUMOCOCCUS INFECTIONS.** Pneumonia, empyema, malignant endocarditis, the complications of otitis media, meningitis are the chief conditions here in question. Pneumococci, like streptococci, vary widely in different strains and autogenous vaccines should be employed. In pneumonia organisms can usually be recovered from the blood but Leary advises vaccines prepared from the sputum. My cases have been too few from which to draw conclusions. The vaccine has been administered every 24 or 48 hours in doses of 10 to 20,000,000 or, as advised by Leary 5,000,000 every 8 or 12 hours. The results reported by Leary (*loc. cit.*) and by Craig (*Medical Record*, 1910, p. 259), are remarkable. It must be remembered of course that we all see desperate cases of pneumonia, get well under indifferent treatment, and that the mortality from the disease varies greatly in different years. Occasional benefit has been seen from vaccines in pneumococcal empyema and the treatment should be tried in all cases with chronic sinuses.

**GONOCOCCUS INFECTIONS.** Dieulafoy has reported two cases of gonococcal septicemia caused by vaccine therapy; gonococci could be cultivated from the blood long after disappearance of symptoms. Miller reported one case cured, Eyre one improved, Irons three not affected. As a rule more is to be expected in the treatment of the chronic rather than the acute in the metastatic rather than the local manifestations of the disease. In the vulvovaginitis of children excellent results have been obtained by Hamilton, Churchill and Soper and others. Hamilton recommends injections of 50,000,000 every 5 days increasing gradually to 100,000,000 and repeating this maximum dose every 10 days. There can be no doubt of the value of the vaccine in chronic gonorrheal arthritis. It is often impossible to obtain an autogenous vaccine and stock preparations from different strains must be employed. The writer has seen definite benefit in a few cases. In recent infections begin with 20,000,000 and increase to 200,000,000 or 400,000,000 fairly quickly if no unfavorable local and general reactions are obtained, injecting every 5 or 7 days. In chronic cases larger doses 500,000,000 to 800,000,000 may be necessary before improvement is noted.

**TYPHOID BACILLUS.** The prophylactic inoculation against typhoid, first introduced by Wright, promises in its modified form to be of great value. The above mentioned article of Russell gives an excellent account of the preparation and administration of the vaccine and of its use in the United States Army. Spooner working under Richardson's direction has inaugurated the routine administration of preventive inoculations to the nurses and house officers in the Massachusetts General Hospital. Russell advocated an initial dose of 500,000,000, a second of 1,000,000,000 in ten days and a third of 1,000,000,000 at the end of 20 days. No very definite results have been reported in the treatment of typhoid. Richardson thinks vaccines properly used will prevent a large percentage of relapses. Other writers think the course of the fever has been milder. The writer has seen no apparent result in some half dozen cases.

I have been able to collect accounts of eight cases

of typhoid carriers reported cured by the use of vaccines. If substantiated by further investigations the importance of the matter can hardly be overestimated. Not only is a check given to the spread of infection but the possibility of control of many cases of chronic typhoid cholecystitis seems offered. In two instances under my observation osteoarthritis of the spine developing not long after typhoid has seemed promptly and decidedly benefited by heterologous typhoid vaccines. In a case of obstinate recurrent bone lesions in which repeated operations had failed to cure an initial dose of 40,000,000 killed typhoid bacilli occasioned a distressing general reaction marked by depression and malaise for days. Subsequently treatment was begun with a dose of 1,000,000 and this was very gradually increased until a dose of 100,000,000 was reached. The affection has apparently been completely controlled.

**COLON BACILLUS.** There are many members of the colon group and whenever possible autogenous vaccines should be used in treatment. Infections of the urinary tract, sinuses persisting after abdominal operations, certain forms of colitis are the conditions most often requiring the use of vaccines. I have seen a fairly large number of acute infections of the bladder and pelvis of the kidney in women and children. It is my impression that such cases get well as quickly under general medical measures and hexamethylenamin as with use of vaccines. In chronic cystitis, pyelitis or pyelonephritis my experience has been that of others—that symptoms are greatly relieved, that in rare instances complete cure results but that usually bacilluria persists. Possibly long continued use of vaccines would finally clear up the infection. Recent work of Michaelis confirms the observation of Wright as to the agglutination phenomena of colon bacilli in the urine under the influence of autogenous inoculations. In a recent series of 30 cases of infection of the urinary tract reported by Hugh Cabot 25 were due to the colon bacillus. Vaccine treatment relieved symptoms in 19 while 11 were uninfluenced. In 27 bacteruria still persisted in 3 instances organisms had disappeared. The frequency with which tuberculosis is found associated with chronic colon infections of the urinary tract must be borne in mind and the proper treatment with mixed vaccines instituted.

I have seen two cases of chronic cholecystitis apparently much benefited by the use of colon bacillus stock vaccines in the past two years. Wright and Reid, Turton and Parkin have reported cure in acute cases of cholecystitis and cholangitis from the use of autogenous vaccines. Favorable results have been reported in the treatment of various diseases of the colon, ulcerative and membranous colitis, and English authors write of benefit to many indefinite symptoms of questionable relation with disturbances of the colon. The initial dose of colon bacillus vaccine should be from 10 to 20 millions. The amount may be increased quickly to 50,000,000 or even 100,000,000—the interval between injections should be from 5 to 7 days.

It is impossible to write of all the conditions in which treatment by vaccines has been recommended. Wynn, Cobb and others have treated actinomycosis successfully. Pyorrhea, asthma, bronchiectasis, acute

nephritis, prostatitis, many skin affections in addition to those just mentioned, common colds, sinusitis—all these have been reported benefited by autogenous or stock vaccines. The writer has seen improvement in two cases of chronic influenza, but variations in the course of this infection may be frequently observed under almost any treatment; in some of the cases regarded as chronic influenza I am of the opinion that the influenza bacillus is merely saprophytic and not the cause of pulmonary symptoms.

The report of Coakley and Kendall upon vaccines in chronic suppuration of the nasal sinuses is not encouraging; that of Reik upon vaccines in otology is equally unenthusiastic. In a series of 40 cases of middle ear suppuration communicated by Miss Nagle working with Cobb of Boston discharge had existed for a few months and in 34 from 1 to 40 years. Cure was obtained in 39! Injections were made at intervals of 3 days of autogenous vaccines sterilized at low degrees of heat in the shortest possible time. On the other hand Dr. Alice Hamilton of Chicago treated a number of cases of middle ear disease following scarlet fever; those treated by vaccines did well but no better than another group of cases with routine cleansing as the only therapeutic measure.

Reports like these make it difficult as yet to pronounce final judgment on the clinical value of vaccines. My own opinion, though not extremely enthusiastic, is that they offer a very decided addition to our resources in the treatment of infections and their complications. There is great need of more careful preparation of autogenous vaccines and of proper clinical supervision of dosage and frequency of administration. The indiscriminate use of stock preparations without proper determination of the nature of the infection is strongly to be condemned. I have seen several cases of syphilitic and tubercular arthritis being treated with gonococcus vaccines. One great danger of the multiplication of easily administered remedies supplied by drug houses lies in the neglect of careful diagnosis. Sober judgment should realize the limitation of the new method and not expect it to displace older forms of treatment. I have seen a patient being treated enthusiastically with vaccines for pneumonia with one side of the chest half full of pus. In another case colon vaccine was being given for the cure of pyuria while a pyelitis was being maintained by calculi in the kidney. Treatment with vaccines must supplement and not supplant well recognized surgical procedures. In light of our present knowledge no one has a right to delay operation on an acute mastoid of pneumococcus origin with the hope that vaccines may cure the infection. The infected gall bladder with cholelithiasis must be operated upon, the appendix abscess opened, the empyema drained before much help can be expected from vaccines.

#### Discussion.

Dr. C. C. Warden, Los Angeles: An expression of personal pleasure and profit derived from hearing Dr. Gay's valuable and timely paper must be my first duty. Coming from a source of such unquestioned authority and immense experience in biologic experimentation, the paper claims added value and distinction. The presentation deals with the sub-

ject historically, critically, and suggestively. The writer has given due credit to Jenner, Pasteur, Pfeiffer and Wright, and to that list should be added Bordet, Gengou and Gay. Wright's method and theory have been presented in clear outline and with very just criticism. The opsonic index as Wright commended it has ceased to be a practical guide to clinical work, but it served to introduce the phagocytic index of diluted sera and the curves to be plotted therefrom; a valuable but still impracticable laboratory method of studying individual immunity response.

As the author states, Wright did not fortify his work with animal experimentation. Were I permitted to select from the paper but one assertion to emphasize, it would be, in his own words, "Animal experimentation offers the only possible method of acquiring a complete series of facts and any consequent deduction as to the cause of biologic phenomena."

What are the principles of vaccine therapy? Allow me to present them as I see them. First, an indifferent, non-specific and natural immunity toward most organisms exists in most of the tissues of the body. Excessive numbers of organisms or increased virulence of bacteria may overcome this immunity but it is this natural cellular immunity and phagocytic activity that make vaccine therapy possible. Second, an infection is primarily local. Even when bacteremia results from a primary focus there are tissues which seem to be elective to bacterial growth, and bacteria are destroyed in, and by, a majority of the tissues. For example, consider pneumococcus or streptococcus sepsis. There is endocarditis and the blood is laden with bacteria, but abscesses in the spleen are almost unknown despite the fact that infective heart emboli find their commonest stopping place there. The same is true of lung, liver, brain and muscular systems. Animal experimentation has shown that it is not the circulating blood of itself which destroys organisms, nor indeed the unfortified leukocytes in it, nor the specific cells of the various tissues (save the hemolymph apparatus) but the endothelial cells of the capillaries in the organs and the fortified phagocytes in the tissues. Third, when bacteria have once come to thrive in a tissue, that tissue is no longer immune, and help will come not from increased destroying power of that tissue but by aid from the other tissues of the body; tissues of the body, not blood itself, for even toxins in the blood rapidly disappear. Toxins in the blood of one animal transfused into another animal produce no antibodies in the recipient, but the original toxin-bearing animal begets antibodies although deprived of its own blood.

These are the main principles, underlying all of which the leukocytes and phagocytosis constitute an active agency. These principles lead us to inject killed or live cultures into an infected individual in a part away from the original site of infection in order to produce, first, a local antibacterial, phagocytic and antibody reaction, followed by a general one. Is it not true that blood infection is, in a sense, a local infection, and that in a tissue which is almost wholly immune to bacterial influence? At any rate it is but a step beyond a local infection and why not administer vaccines for this infection as well as another. It is not irrational, on careful examination. The subcutaneous tissues which we inoculate are seldom attacked in general infections. They constitute a large, local lymphatic storehouse and laboratory, admirably detached, and fitted as a factory for antibody and phagocytic activity.

Granted then, that vaccine therapy is indicated in local infections, and bearing with me in the contention that vaccines are applicable in the other extreme (sepsis), what disposition is to be made of those infections with profound toxin exhibition like pneumonia, typhoid, etc.? In these infections the fatal event is either from accidental causes like hemorrhage or heart failure or complications or is determined by toxic action on nerve centers rather

than by exhaustion of the tissues. Paralysis and exhaustion of the tissues are shown by lowering of the body temperature. Temperature itself, barring hyperpyrexia, is an index of healthy tissue response to a toxin. Give vaccines in small quantities into subcutaneous tissues in conditions where temperature is normal or within limits above normal. The system benefits by the slight rise of temperature following such inoculation.

On the other hand, a purely local and very slight infection may be accompanied by profound intoxication, an intoxication as profound, or more so, and as sudden and overwhelming, as may occur in pneumonia, typhoid and septicemia. Vaccines are contra-indicated in all infections where intoxication is so heavy as to have produced tissue exhaustion, shown by feeble and failing pulse and lowered temperature and vitality. In such cases, truly, vaccines only add fuel to the fire.

### THE SURGICAL SIGNIFICANCE OF PAPILLOEDEMA.\*

By LEON WALLACE MANSUR, M. D., Los Angeles.

The subjects of papilloedema and intercranial pressure from all causes, with decompressive operations for these conditions, have been so much written about in all the medical journals during the last few years that we are all more or less familiar with them.

Bordley<sup>1</sup> says that next to headache, choked disc or papilloedema is the most common symptom of brain tumor. Mr. Leslie Paton<sup>2</sup> in an analysis of 200 of his cases found papilloedema in 80%. De Schweinitz<sup>3</sup> found it in 85% of his cases. Other surgeons agree with them so closely that we can safely state that 80% at least of all cases of increased intracranial pressure probably have papilloedema.

The surgical significance of papilloedema is that we have to do with an increase in intracranial pressure from some cause, as new growth, abscess, cyst, hemorrhage, etc., and that unless the tension is relieved before destruction to the brain tissue and nerves occurs, the results of this destruction will become permanent and we will have various paralyses depending on the part of the brain involved, and blindness from the pressure on the optic nerves. For this latter reason the early recognition of papilloedema is of so much importance to both the patient and to the surgeon that too much cannot be said of having an early fundus examination in every suspected case.

It is now a pretty well recognized fact that the condition we know as choked disc or papilloedema is a simple edema of the optic nerve and is caused by intracranial pressure. I can best describe this condition by quoting directly from Mr. Leslie Paton's<sup>4</sup> paper on the pathology of papilloedema:

"This edema is due to two factors, venous congestion and obstruction of lymph outflow. The venous congestion is due to the rise in intravenous pressure which takes place in the central vein to correspond to the raised sheath pressure which in its turn is due to the raised intracranial pressure. Beyond the lamina cribrosa the central vein with raised intravenous tension comes to a tissue no longer subject to raised sheath tension (the vitreous) and the disproportion between intravenous tension and tissue tension leads to increased exudate of lymph. At the same time the drainage of lymph

from the disc is interfered with by the increased sheath tension and a consequent accumulation of lymph in the disc tissue takes place."

Shieck<sup>5</sup> from his observations and experiments agrees that there is no inflammatory process in the nerves, but that it is a simple edema. He further states, however, that the simple raising of the intracranial pressure will not produce the lesion alone, but that there must be also an increase in cerebrospinal fluid. This latter does not seem absolutely necessary to us, as the normal amount of cerebrospinal fluid present might be sufficiently compressed by a very large or rapidly appearing tumor. In fact, Bordley and Cushing<sup>6</sup> state in their experimental work that it may be caused "by transmission of pressure to the fluid already present," and later on in the same article that they produced the same results by digital compression on the dura through a trephine opening, and within the course of a few minutes observed a swelling of two dioptries occur in the nerve head.

Shieck also says that when fluid is injected into one side of the skull the fundus on that side is most violently and first affected. As regards the surgical significance of papilloedema this last statement is of the greatest importance to the surgeon, as when it comes to opening the skull for the relief of the tension and removal of the tumor, everything which can help us in localizing this tumor must be most carefully considered.

Fortunately we would ordinarily have paralyses and other symptoms in various parts of the body which would unquestionably aid us in our localization, and we would not be dependent on the eye symptoms alone.

Bordley and Cushing<sup>7</sup> in their experiments with the injection of fluids into the sub-dural space say they have seen the edema of the disc occur first in the opposite eye and later followed by equal changes in the homolateral eye. Sir Victor Horsley<sup>8</sup> says nothing less could have been expected from the Manz method (injection of fluid) which they employed. He thinks that while this introduction of fluid is of the greatest importance as the mechanical factor in producing the lesion, that we cannot rely absolutely as to which side it will first occur on. Sir Victor Horsley<sup>9</sup> was one of the first to call attention to the fact that the papilloedema was first seen on the homolateral side and that the greatest amount of involvement to the nerve was also homolateral. He thinks that in nearly every case the side on which the tumor is located can be determined by a careful examination of the fundus changes.

Paton<sup>10</sup> in an analysis of 252 cases found 84% on the homolateral side, but on account of the 16% contralateral thinks we cannot be sure from this alone. De Schweinitz<sup>11</sup> and Holloway say that in the majority of their cases the greatest amount of swelling was on the homolateral side, but that with Horsley, Cushing, Bordley and others they agree that other things besides the swelling must be taken into consideration.

We must carefully examine the fundus as to which nerve was probably first affected; the position of the swelling will here help us as it occurs first in

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